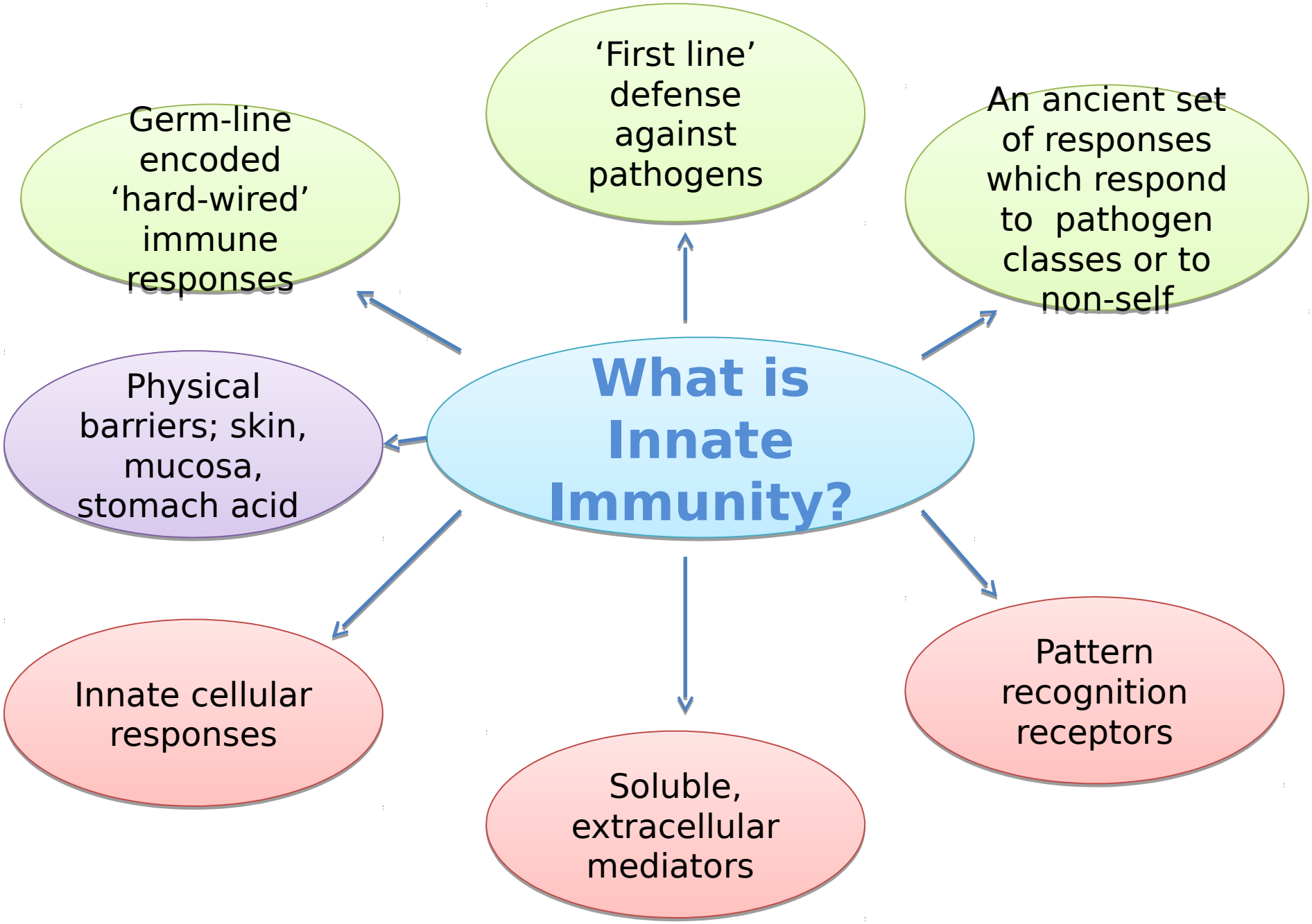
Introduction to Innate Immunity

Part II Immunology in Pathology

Dr Brian Ferguson

08/10/2015


What is Innate Immunity?
'First line' defense against pathogens
Germ-line encoded 'hard-wired' immune responses
An ancient set of responses which respond to pathogen classes or to non-self
Physical barriers; skin, mucosa, stomach acid
Innate cellular responses
Soluble, extracellular mediators
Pattern recognition receptors

Innate

vs

“ready to go”
(constitutive)
recognises conserved
pathogen features
(PAMPs)

required for adaptive
response

some diversity
some specificity
“evolutionary
memory”

Adaptive

“needs time” (inducible)
recognises everything
(randomly generated
then selected)

requires innate response

enormous diversity
exquisite specificity
“somatic memory”

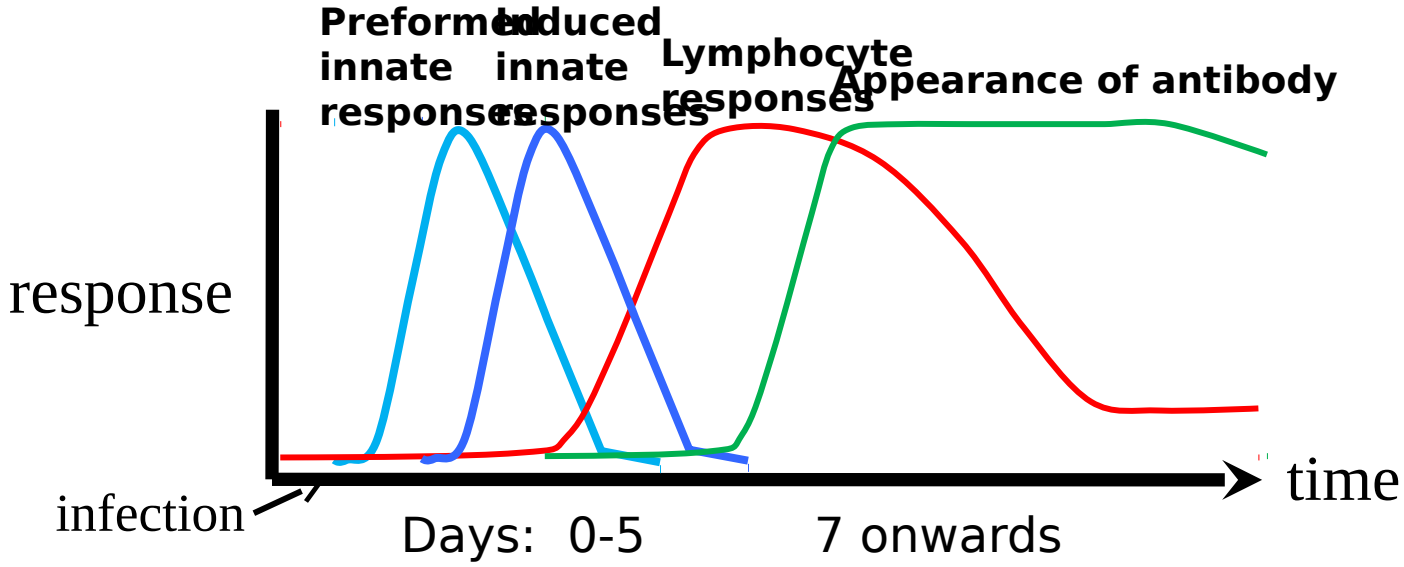
Where is innate immunity?

- Everywhere
- All cells – pattern recognition is ubiquitous
- All organisms have innate defenses

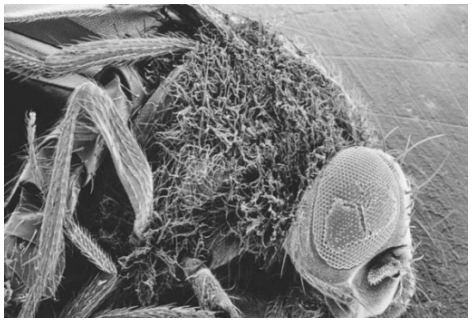
Why do we need innate immunity?

- Initial defense mechanisms
- Starts the overall immune response
- Drives adaptive immunity

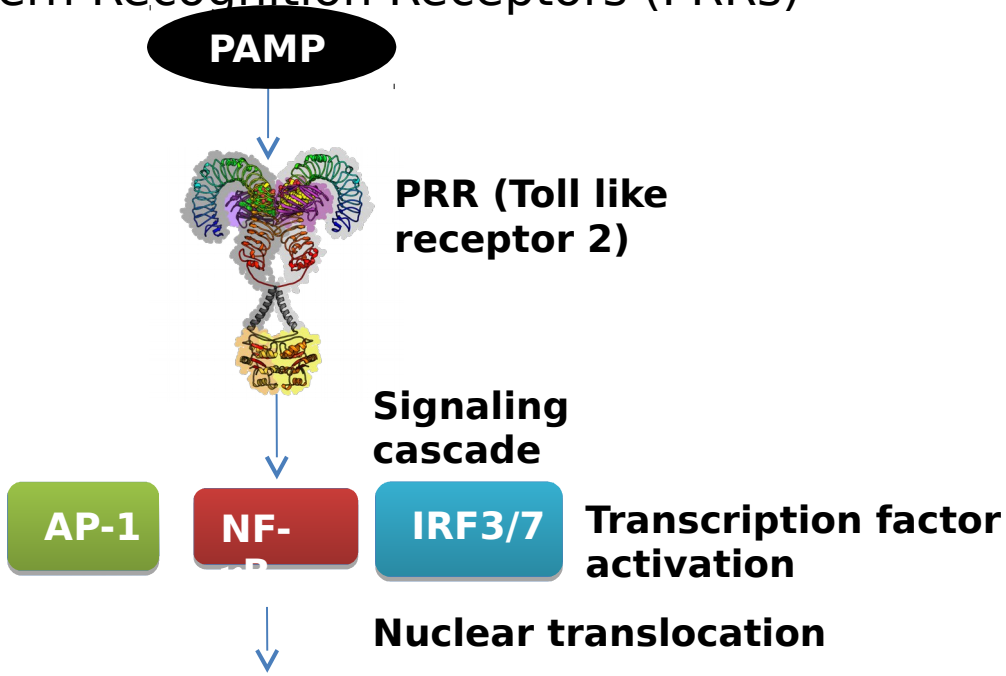
Generic mammalian immune response



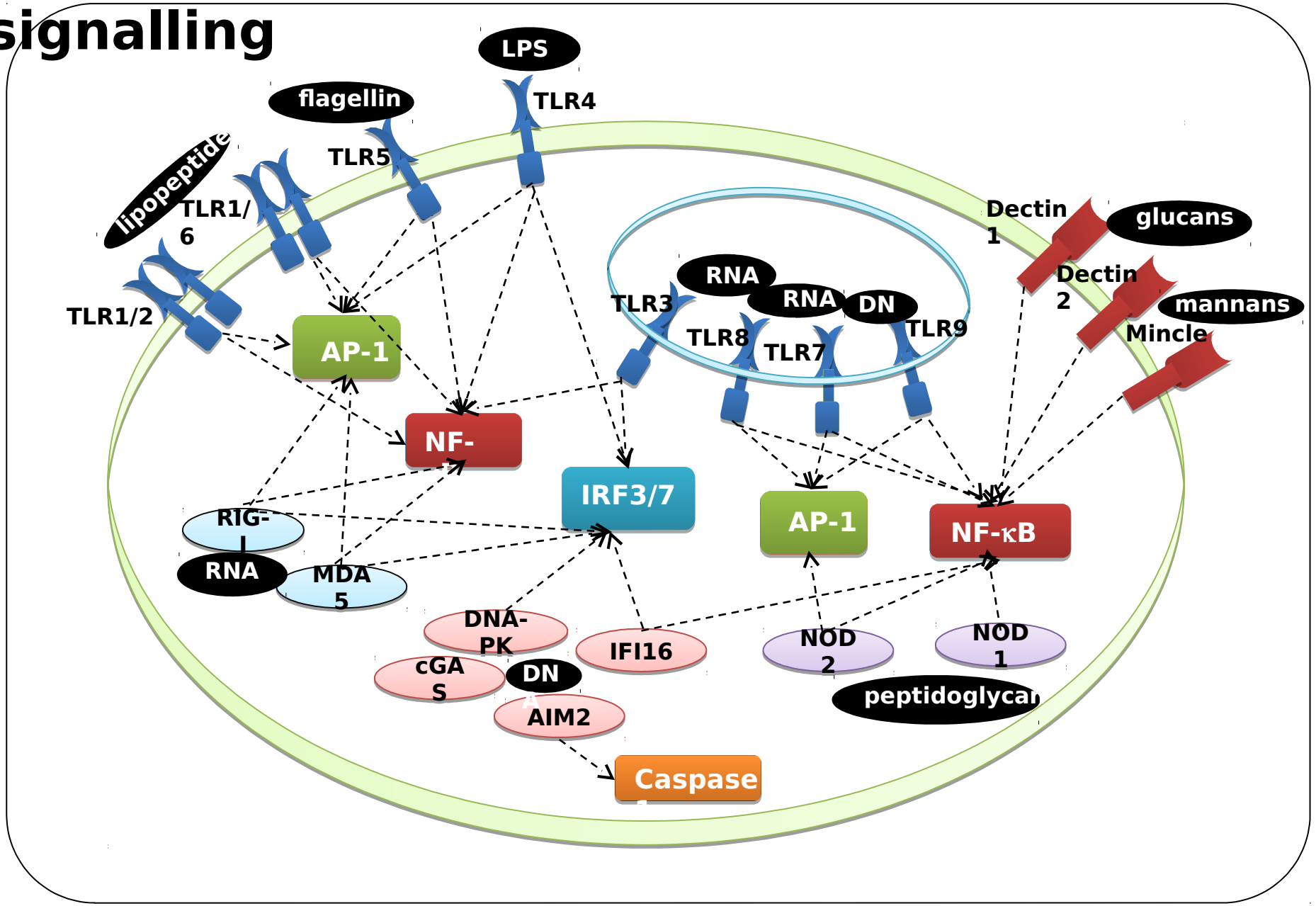
Pattern recognition



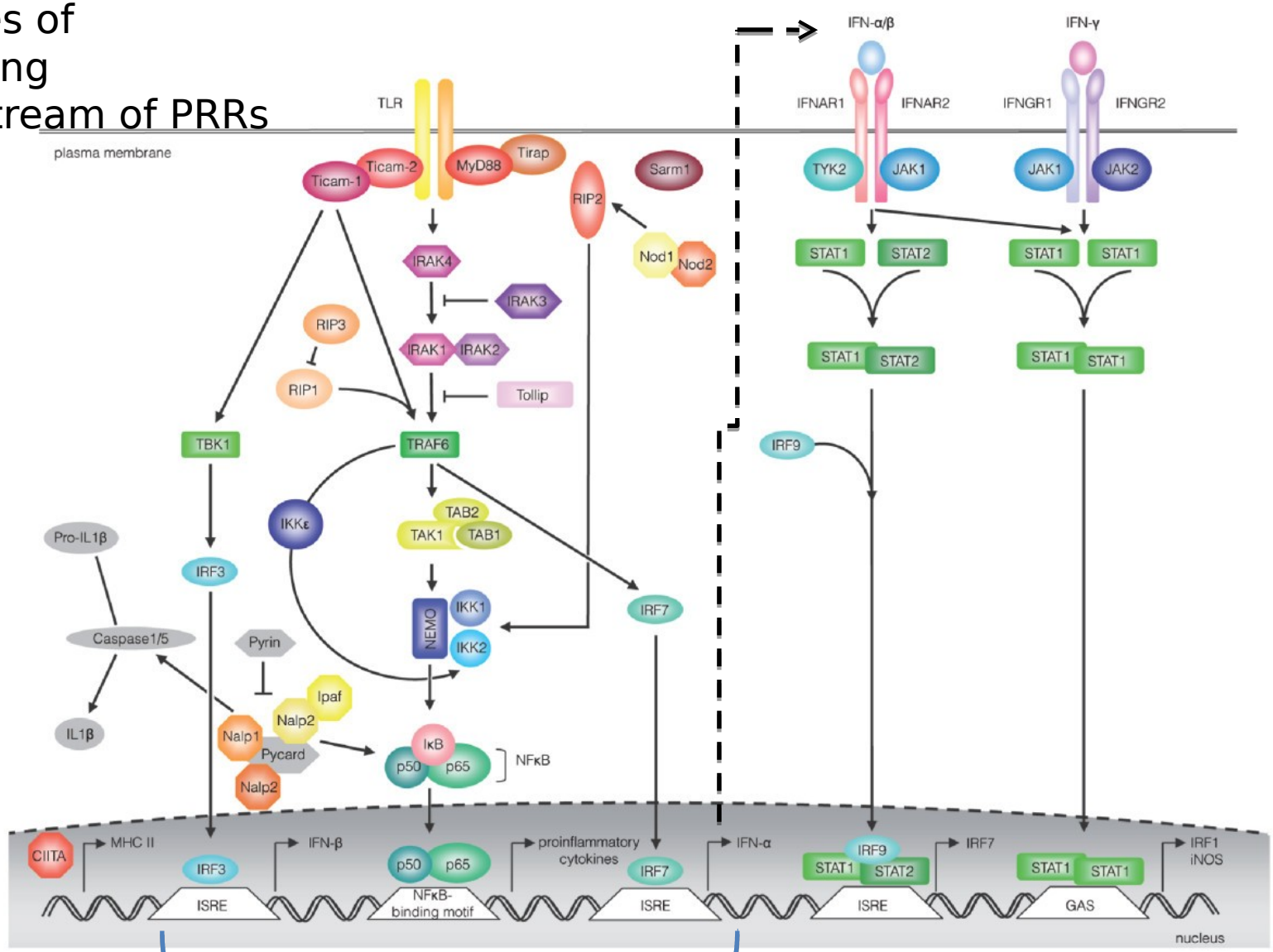
- Receptors bind to ligands that are parts of pathogens (PAMPS)
- Initiate pro-inflammatory signalling pathways
- Receptors are Pattern Recognition Receptors (PRRs)



Pattern recognition receptor signalling



2 waves of signalling downstream of PRRs



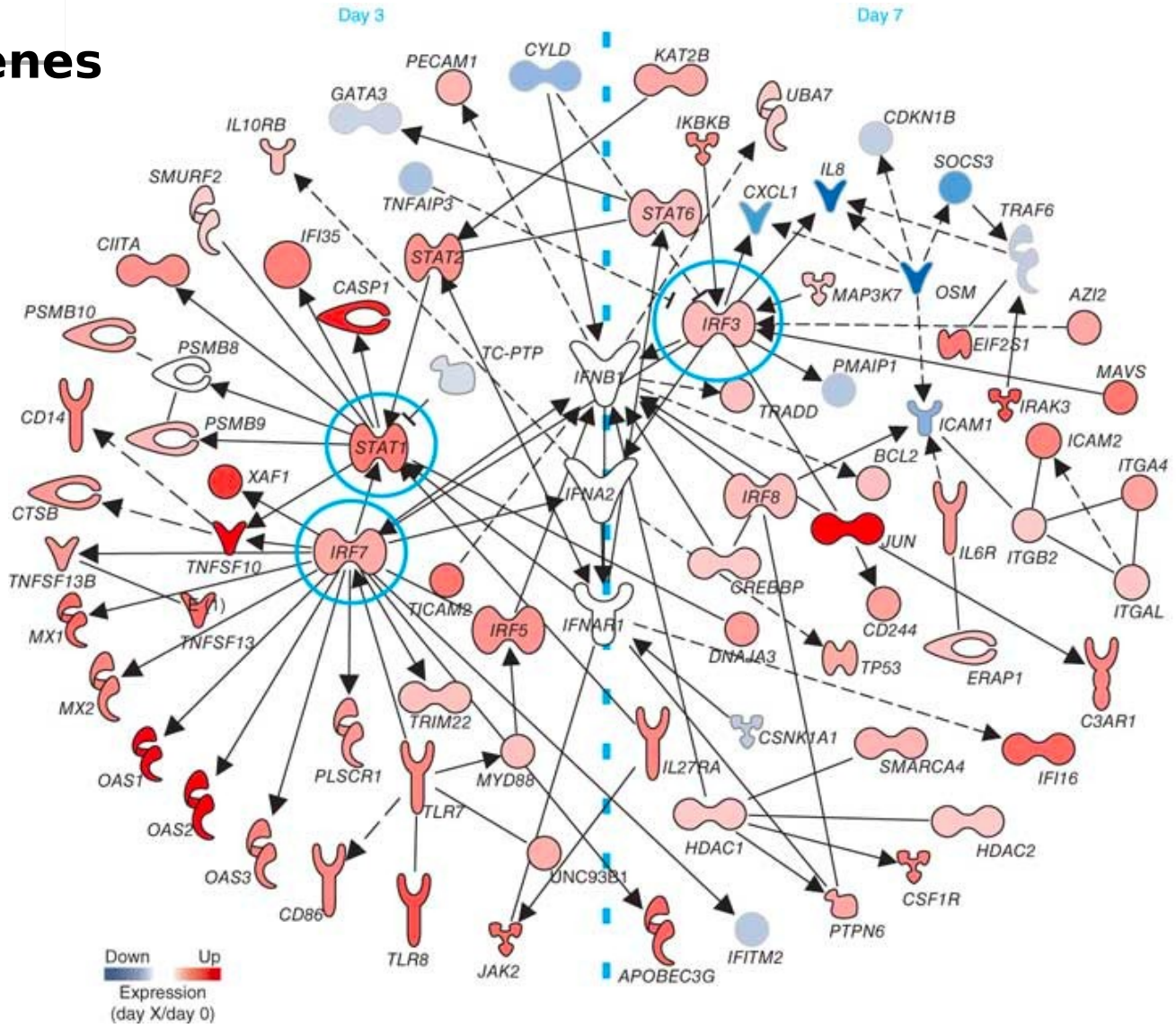
Cytokines/chemokines + interferons

Cell intrinsic anti-viral factors

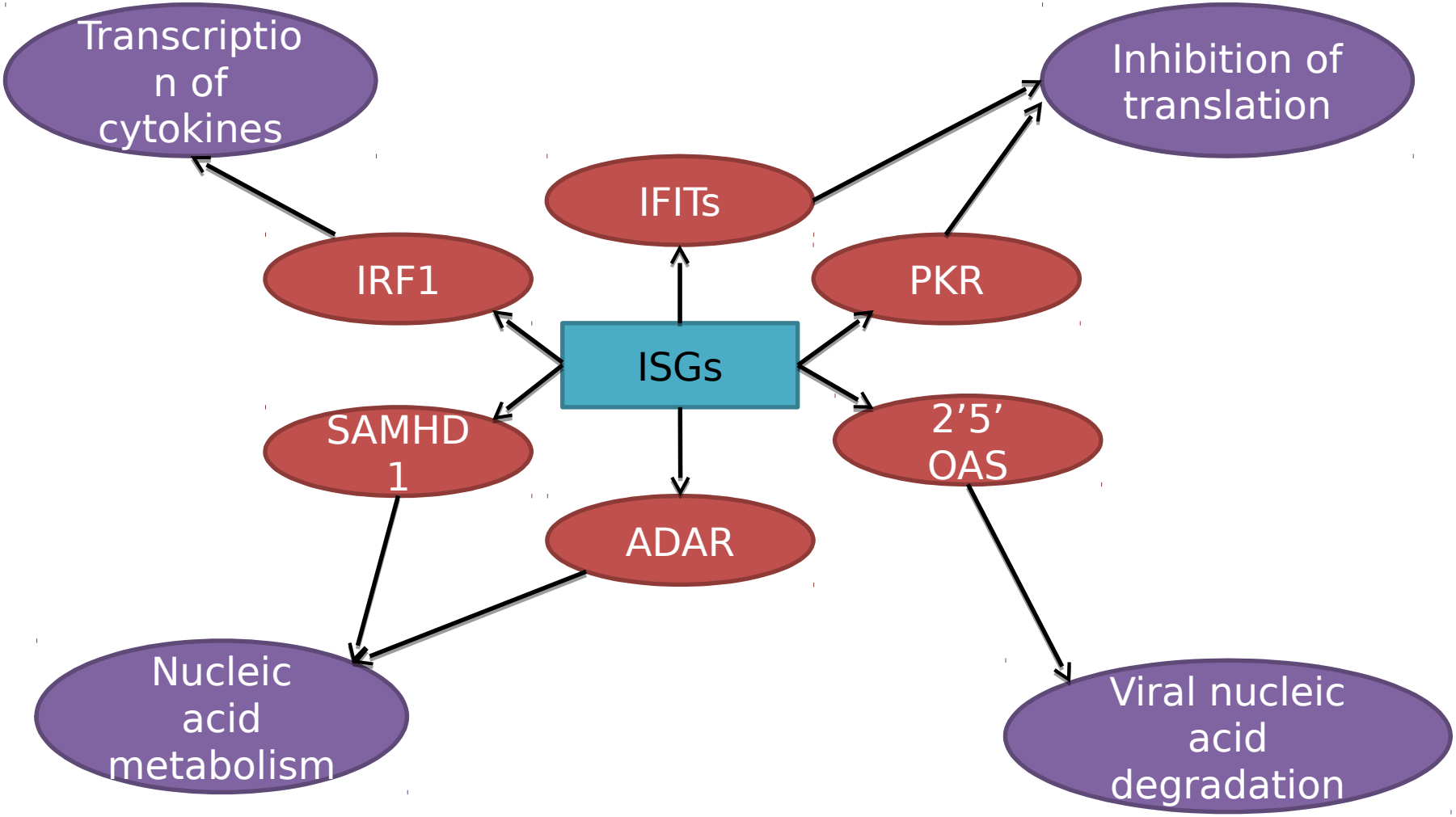
in et al. Genome Biology 2007 8:R251

Interferon stimulated genes

Hundreds of cell intrinsic anti-viral proteins that enable an ‘anti-viral’ state inside cells surrounding site of infection

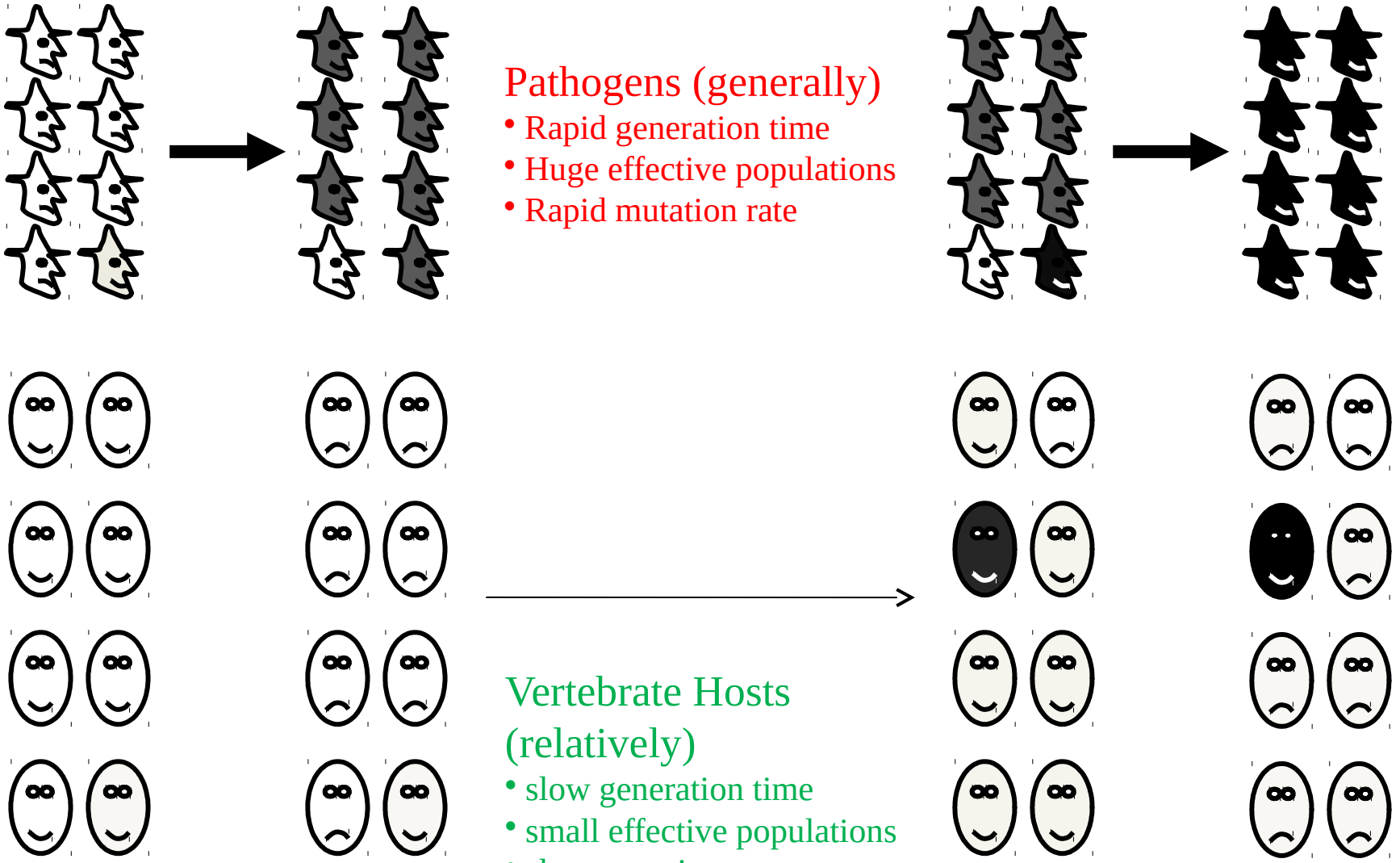


Interferon stimulated genes



Why are these systems so complex?

gens and hosts are locked in an evolutionary molecular arms



Pathogens (generally)
- Rapid generation time
- Huge effective populations
- Rapid mutation rate

Vertebrate Hosts (relatively)
- slow generation time
- small effective populations
- slow mutation rate

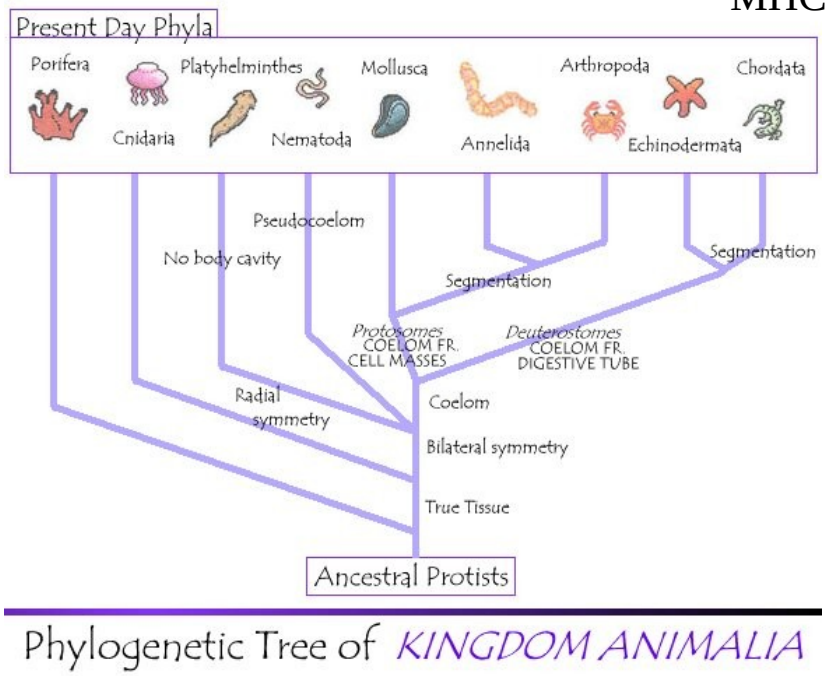
Thanks to Prof Jim Kaufmann

Why are these systems so complex?

- All organisms have innate defense mechanisms, all are complex and diverse
- Complexity is driven by exposure to equally diverse and evolving pathogens
- The key is generation of diversity and there are many different solutions to this problem

Only innate immunity?

Ab
TcR
MHC



Phylogenetic Tree of *KINGDOM ANIMALIA*

All still exist so immunity must work

co-evolution is critical

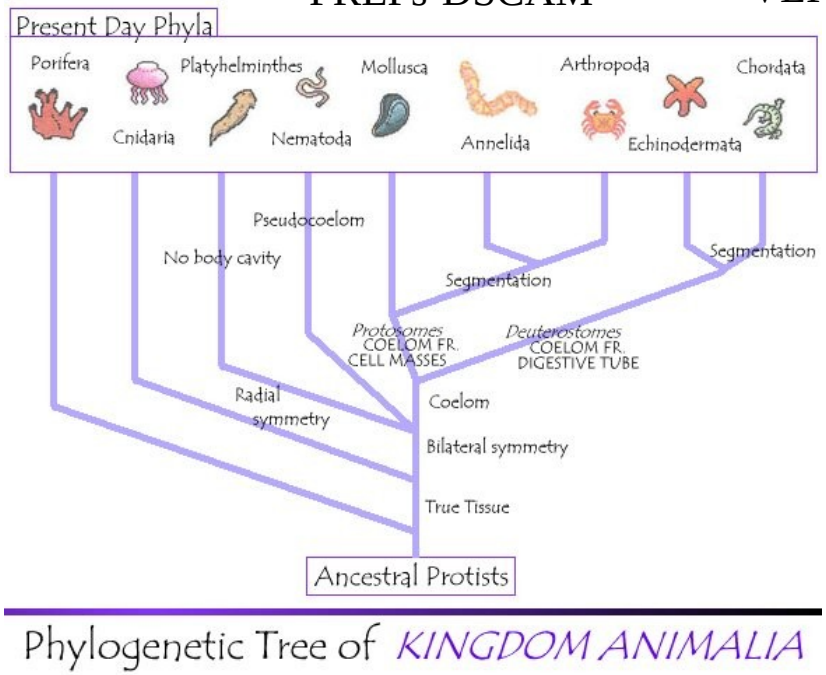
pathogen may become more or less virulent in order to balance replication with

Many ways to generate diversity

Ab
TcR
MHC
and
VLRs

TLRs

FREPs DSCAM



Phylogenetic Tree of *KINGDOM ANIMALIA*

Actually, invertebrates can have their own adaptive immunity and massive genetic diversity in innate receptors

cyclostomes

(lampreys *Petromyzon*, hagfish *Myxine*)
variable lymphocypte receptors (VLRs)
(made of leucine-rich repeats, LRR)

- Pancer et al 2004 Nature 430: 174
- Cooper and Alder 2006 Cell 124: 815

echinoderms

(purple sea urchin *Strongylocentrotus purpuratus)*
toll-like receptors (TLRs)

- Rast et al 2006 Science 314: 952
- Hibino et al 2006 Devel Biol 300: 349

molluscs

(snail *Biomphalaria glabrata*)
fibrinogen-related proteins (FREPs)

- Adema et al 1997 PNAS 94: 8691
- Zhang et al 2004 Science 305: 251
- Mone et al 2010 PLoS Negl Trop Dis 4: e813

insects

(fruit fly *Drosophila melanogaster*)
Down syndrome cell adhesion molecule (DSCAM)

- Watson et al 2005 Science 309: 1874
- Dong et al 2006 PLoS Biology 4: e246

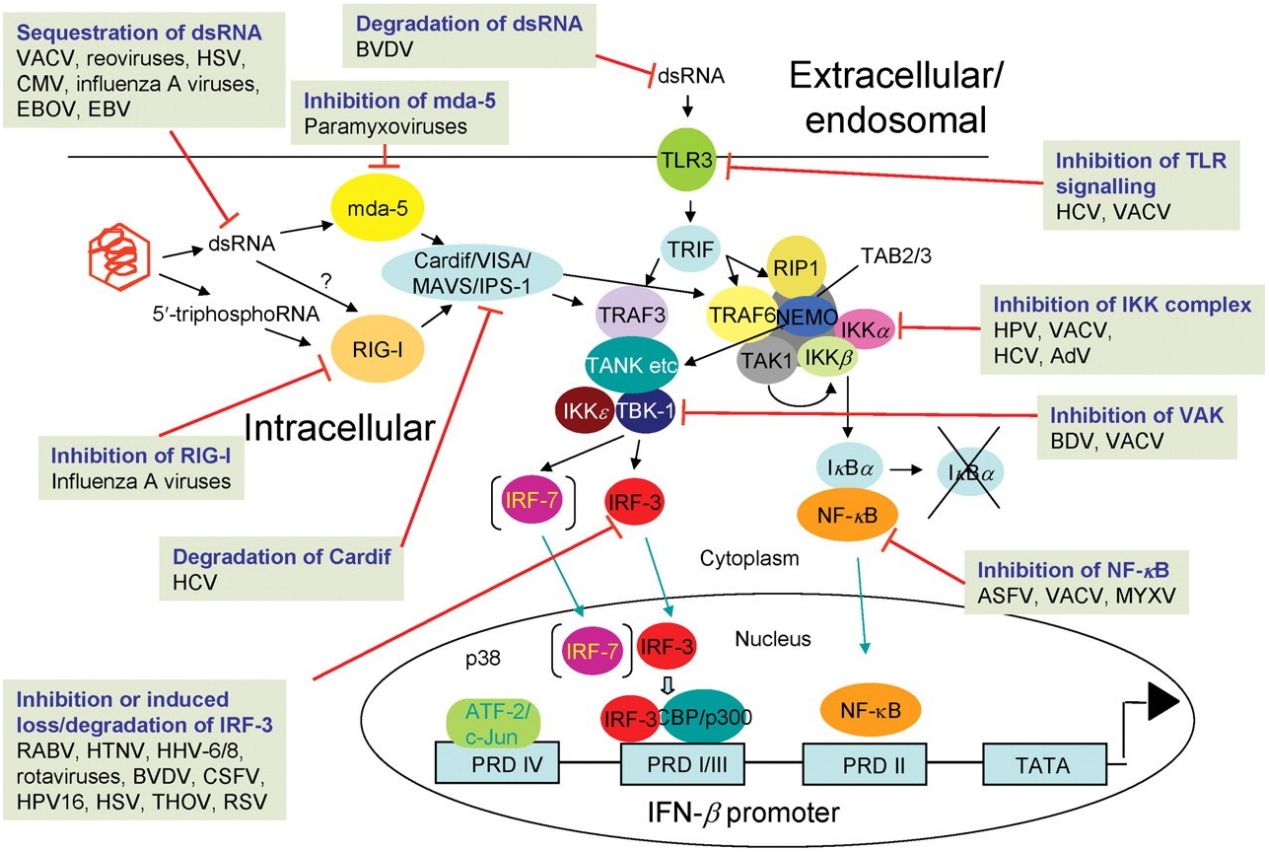
Immune evasion mechanisms

- Pathogens use their own counter-measures to block host immunity
- These mechanisms induce greater complexity over time
- But also result in co-evolutionary balance of host/pathogen interactions

Immune evasion mechanisms

All pathogens make countermeasures

Viruses commonly target PRR signalling to block interferon production



J Gen Virol January 2008 vol. 89 no. 1 1-4

Immune evasion mechanisms

Bacteria are prime targets for opsonisation and phagocytosis

Innate immune responses include eating by macrophages and neutrophils

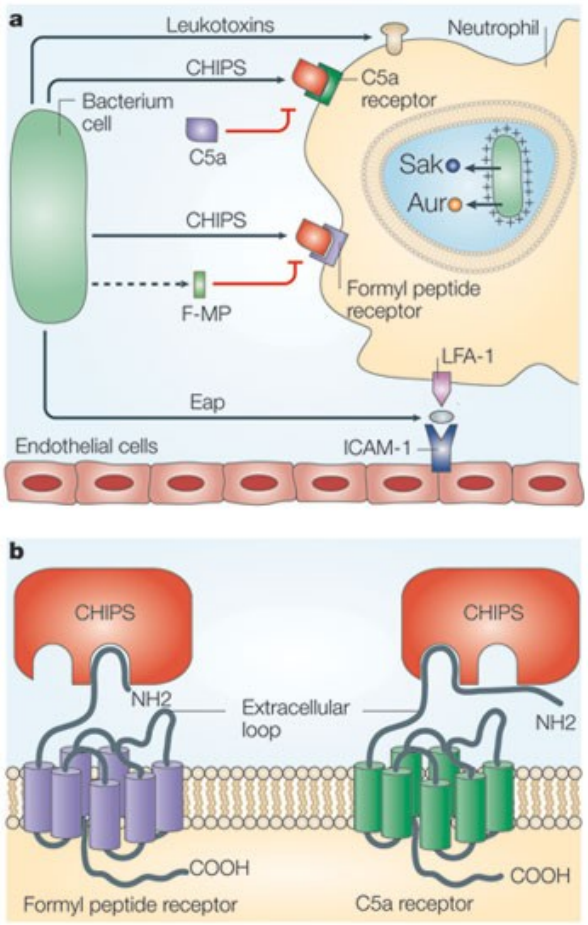
And complement mediated opsonisation and destruction via the complement cascade in the bloodstream

The neutrophil relentlessly chases the *Staphylococcus aureus* bug

The chemotaxis is probably mediated by complement fragment C5a

avid Rogers, Vanderbilt University c.1952

Immune evasion mechanisms



Streptococcus evades complement, phagocytosis and chemotaxis using CHIPS and eap proteins

Immune evasion mechanisms

Schistosoma mansoni

- Causes the parasitic disease schistosomiasis, or Bilharzia. Schistosomiasis affects over 200 million people worldwide
- Adult worms migrate to liver where they lay eggs
- Schistosoma eggs actively secrete immunomoduatory compounds
- Schistosoma egg antigen contains some of the most powerful Th1/Th2 polarising agents
- One protein, the T2 ribonuclase omega-1, can polarise DCs to Th2
- The Th2 environment in the liver assists the co-existence of host and pathogen

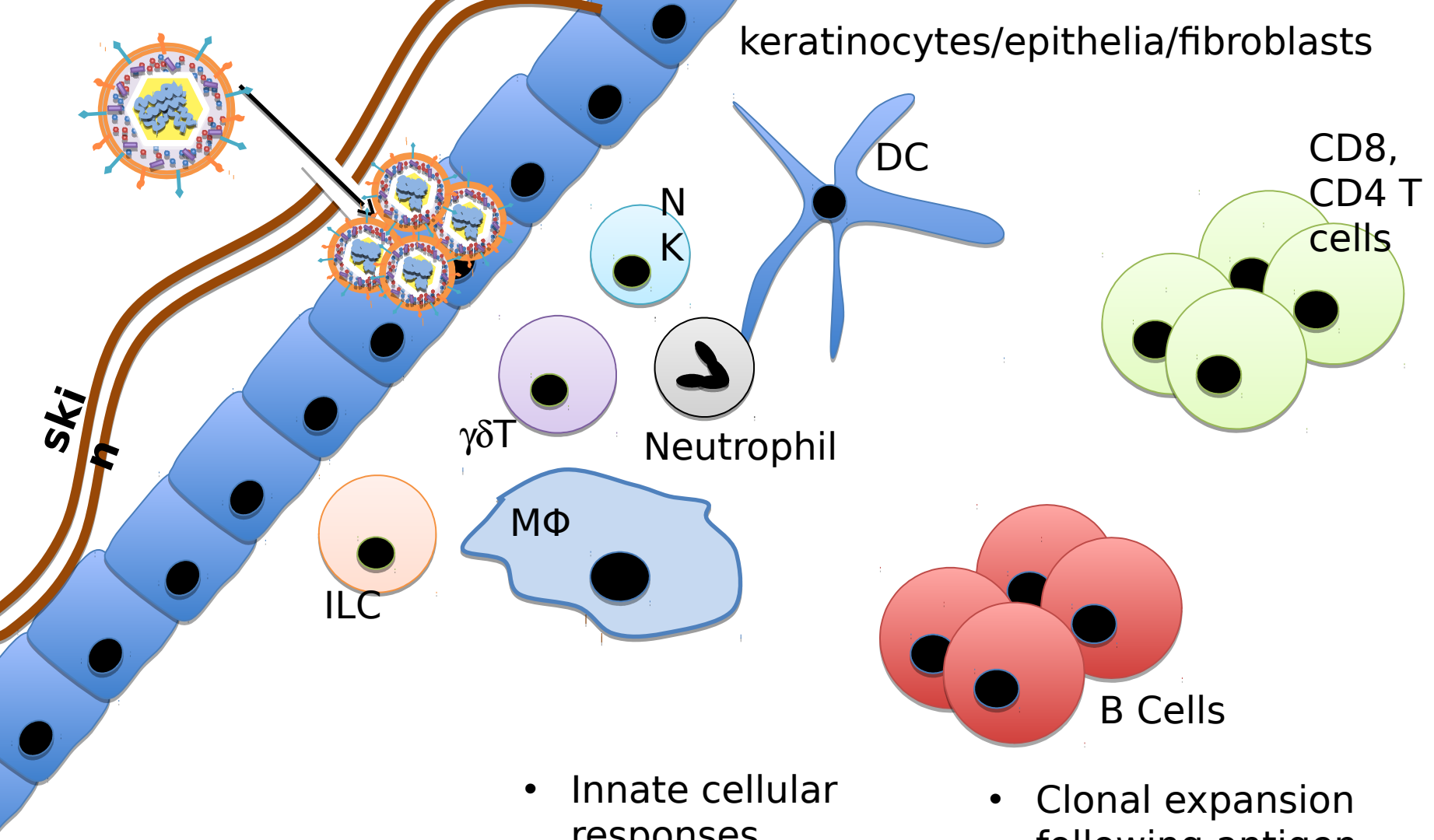
Not just PAMPs but also DAMPs

The detection of damaged tissue is intrinsically linked to the detection of infection

The same PRRs that detect infection can also sense damaged tissue and ha

TLR	Ligand DAMP	Ligand PAMP
TLR1		Triacyl lipoproteins
TLR2	Heat Shock proteins	Peptidoglycan
	HMGB1 (high mobility group box 1—amphoterin)	Lipoprotein
		Lipoteichoic acid
		Zymosan
TLR3	Self dsRNA	Viral dsRNA
TLR4	Heat shock proteins	Heat shock proteins
	Fibrinogen	Lipopolysaccharides
	Heparan sulfate	RSV fusion protein
	Fibronectin	MMTV (Mouse mammary tumor virus) envelope proteins
	Hyaluronic acid	Paclitaxel
	HMGB1	
TLR5		flagellin
TLR6		Lipoteichoic acid
		Triacyl lipoproteins
		zymosan
TLR7/TLR8	Self ssRNA	Viral ssRNA
TLR9	Self DNA	Bacterial and viral DNA
TLR10		
TLR11		Profilin

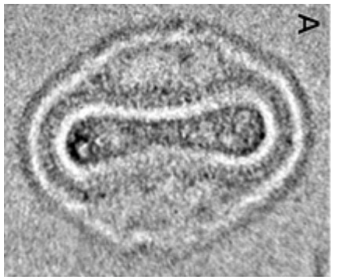
DAMP detection can be sterile or enhance pathogen-induced inflammation



- Inflammation
- Pattern recognition
- Molecular innate defenses

- Innate cellular responses
- Phagocytosis
- De-granulation
- Granulocytes, myeloid cells, innate lymphocytes

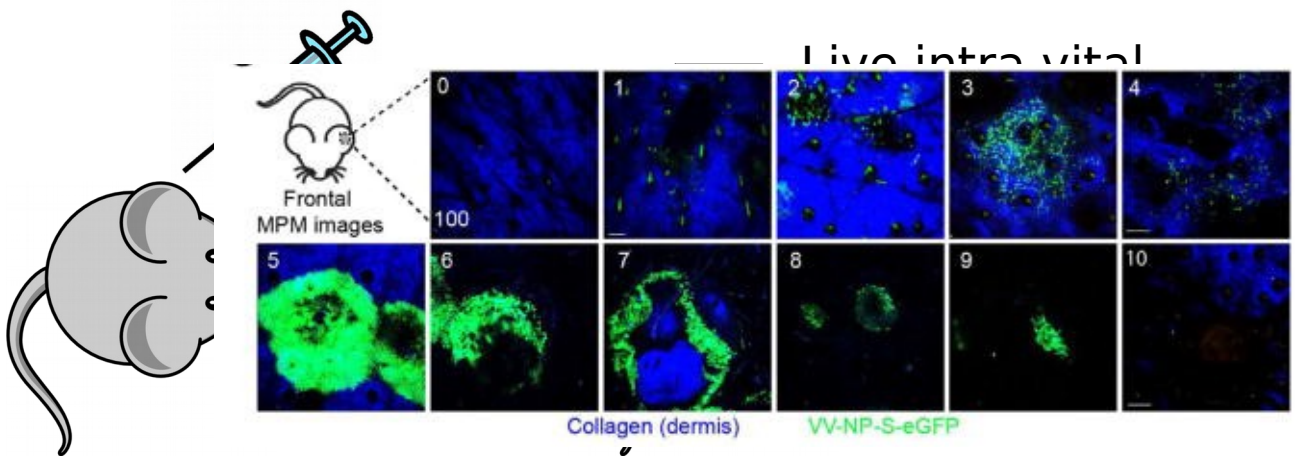
- Clonal expansion following antigen presentation
- T and B cells
- Gene rearrangement
- Permanent immune memory



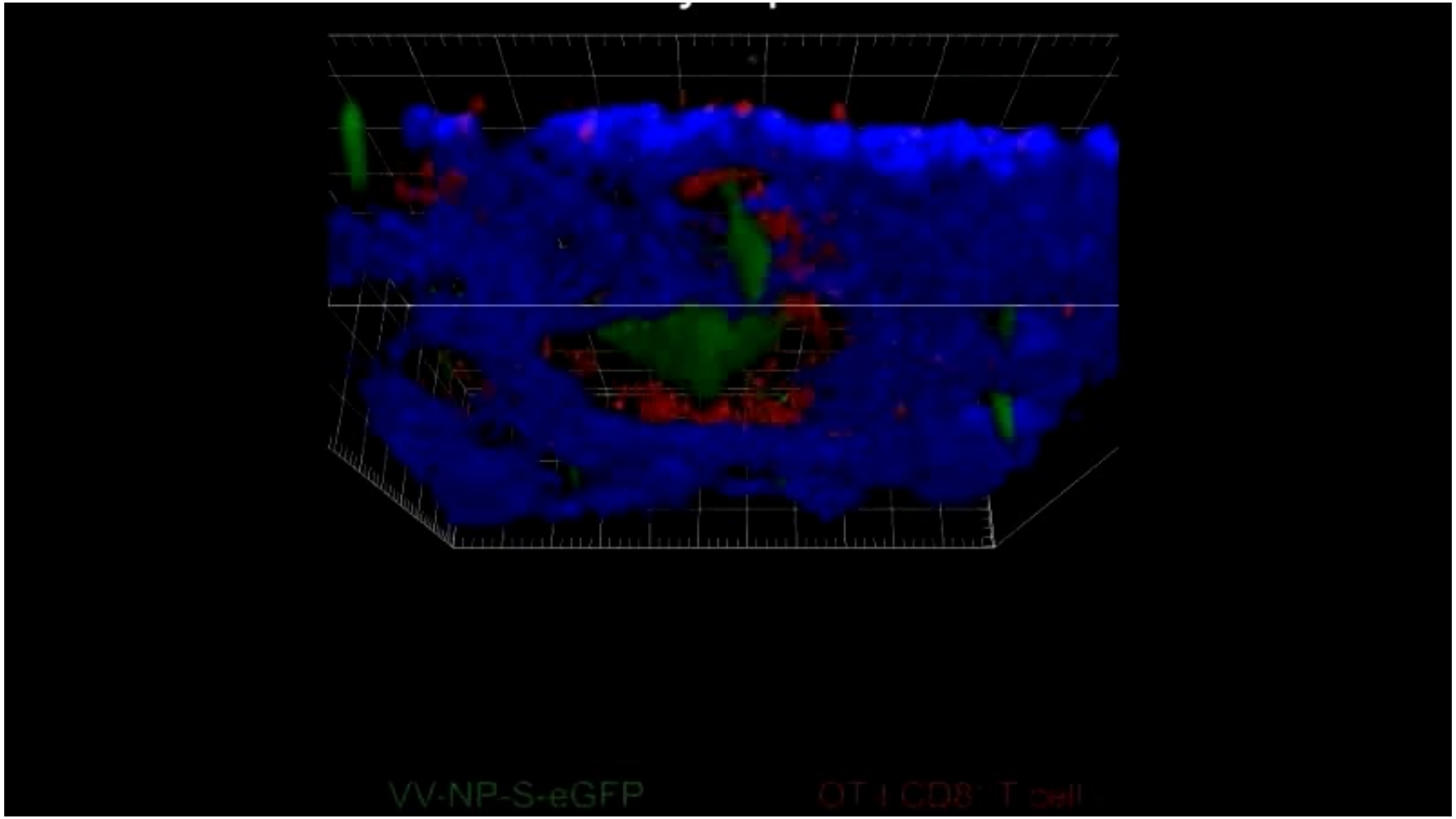
Vaccinia virus – large double strand DNA poxvirus

Related to variola and used as vaccine to eradicate Smallpox as vaccination with is non-pathogenic in humans vaccinia but provides cross-protection against variola

Model for vaccination is intradermal infection in mouse ear.



http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3591514/figure/F1/



l Host Microbe. 2013 Feb 13;13(2):155-68

What happens when innate immunity is impaired?

Lack of an appropriate innate immune response can be devastating – but can also be more subtle than at first consideration

Information can be obtained from rare human primary immune deficiencies.

NK cell deficiency

Autosomal recessive CD16 mutation, which leads to a functional NK cell deficiency and autosomal dominant GATA2 mutation, which leads to classical NK cell deficiency.

Patients with these deficiencies suffer from multiple severe virus infections

TLR3 deficiency

Children with mutations in TLR3, TRIF, TRAF3, all suffer (only!) from severe herpesvirus infections

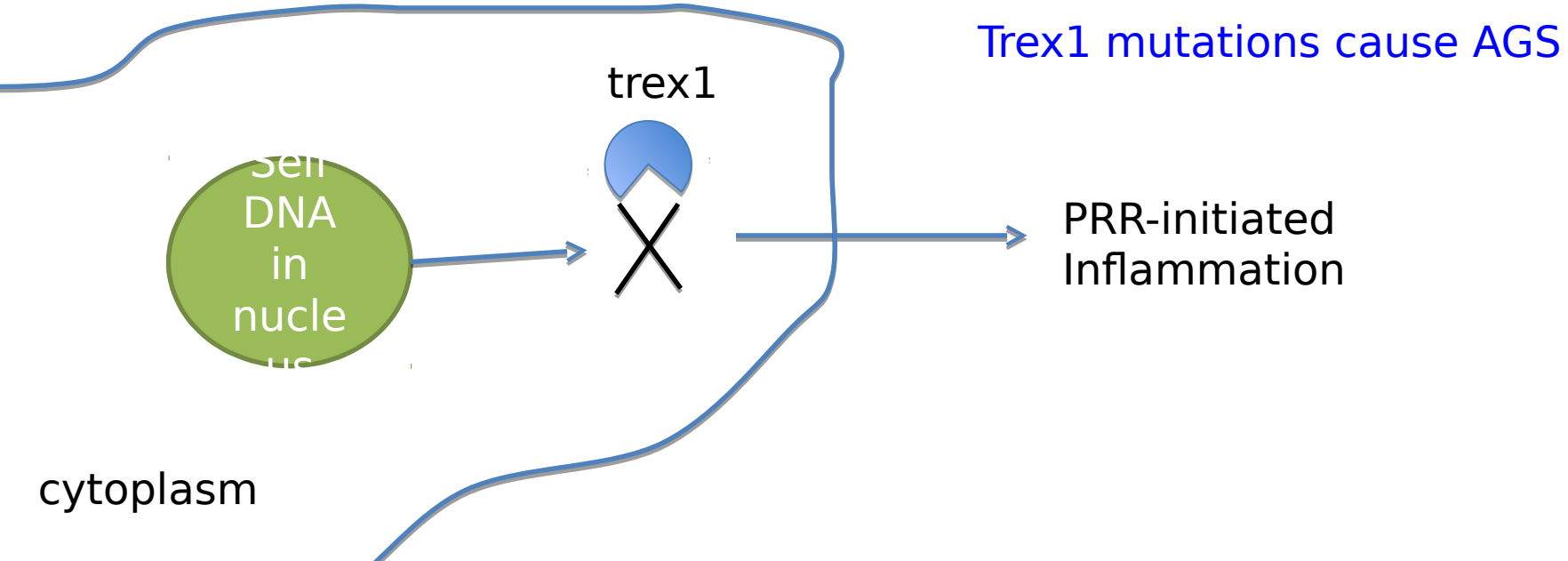
What happens when innate immunity is impaired?

DAMPs can drive sterile inflammatory responses

But dysregulation of such responses can lead to autoimmune disease

Self DNA in the wrong compartment can activate inflammation and interferon production (mechanisms next week!)

Defects in clearance of this self-DNA result in systemic auto-inflammation – Aicardi-Goutiere's syndrome



Take home messages

- Innate immunity is ubiquitous and essential for life
- It has evolved side-by-side with pathogens resulting in a complex system of alarms and responses
- Many aspects of innate immunity are relatively new and so you are learning at the edge of human knowledge
- Not all the answers are fully formed so you require critical analysis of data to make up your own minds about the information being presented
- Learn the basics and dig deeper into the concepts that interest you